KING & SPALDING

1730 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, D.C. 20006-4706
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3383 '99 NOV 19 P4:36

November 19, 1999

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 106 1
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this Citizen Petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. 355(j)(2)(C)), which authority has been delegated to the Commissioner of Food and Drugs under 21 C.F.R. § 5.10. Petitioner requests the Commissioner of Food and Drugs to make a determination that the drug products hereinafter described are suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

King & Spalding requests a determination that a drug product containing 9.25 mg oxycodone hydrochloride, 0.85 mg oxycodone terephthalate, and 650 mg acetaminophen, and a drug product containing 7.0 mg oxycodone hydrochloride, 0.57 mg oxycodone terephthalate, and 500 mg acetaminophen in a tablet for oral administration are suitable for evaluation under an ANDA.

B. Statement of Grounds

The FFDCA allows an ANDA applicant to petition FDA for permission to file an ANDA for a drug product whose strength differs from that of the listed drug. See 21 U.S.C. § 355(j)(2)(C); 57 Fed. Reg. 17950, 17952 (1992). In addition, the FFDCA allows an ANDA applicant to petition FDA for permission to file an ANDA for a combination drug product with one different active ingredient from the listed drug. Id.

The reference listed drug upon which this petition is based is Endo Pharmaceuticals' 4.5 mg oxycodone hydrochloride, 0.38 mg oxycodone terephthalate, and 325 mg aspirin in a tablet for oral administration. Approved Drug Products with Therapeutic Equivalence Evaluations 18th Edition ("The Orange Book"), p. 3-33 (NO7337 006). In addition to the reference -drug, the Center for Drug Evaluation and Research has already approved Endo

C99P-5105

CP1

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ATLANTA, GA 30303-1763
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TELEPHONE: 212/556-2100
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1100 LOUISIANA STREET, SUITE 3300
HOUSTON, TX 77002-5219
TELEPHONE: 713/751-3200
FACSIMILE: 713/751-3290

Pharmaceuticals' 2.25 mg oxycodone hydrochloride, 0.19 mg oxycodone terephthalate, and 325 mg aspirin, id. (NO7337 005), Endo Pharmaceuticals' 10.0 mg oxycodone hydrochloride and 650 mg acetaminophen, as well as Endo Pharmaceuticals' 7.5 mg oxycodone hydrochloride and 500 mg acetaminophen. The approval letter for these products is attached. (Attachment 1). Thus, there are currently on the market split salt products (containing oxycodone hydrochloride and oxycodone terephthalate) combined with aspirin, as well as oxycodone products combined with 650 mg or 500 mg acetaminophen. The Center for Drug Evaluation and Research has also recently approved a suitability petition for 4.5 mg oxycodone hydrochloride, 0.38 mg oxycodone terephthalate, and 325 mg acetaminophen; as well as 2.25 mg oxycodone hydrochloride, 0.19 mg oxycodone terephthalate, and 325 acetaminophen in a tablet for oral administration. The petition approval letter is attached. (Attachment 2). The approval of this suitability petition demonstrates the Center for Drug Evaluation and Research's willingness to replace aspirin with acetaminophen in an oxycodone split salt product. We have attached a table listing products similar to the proposed product that have been approved or for which suitability petitions have been approved.

The proposed products are similar to the reference product in that the proposed products contain oxycodone hydrochloride and oxycodone terephthalate in combination with a proven analgesic. The proposed products differ from the reference product in that instead of the 4.5 mg oxycodone hydrochloride, 0.38 mg oxycodone terephthalate, and 325 mg aspirin, the proposed products contain 9.25 mg oxycodone hydrochloride, 0.85 mg oxycodone terephthalate, and 650 mg of acetaminophen or 7.0 mg oxycodone hydrochloride, 0.57 mg oxycodone terephthalate, and 500 mg acetaminophen. The 9.25 mg / 0.85 mg / 650 mg product is similar to Endo Pharmaceuticals' approved 10 mg oxycodone / 650 mg acetaminophen, in that both products contain 8.96 mg of oxycodone base. The 7.0 mg / 0.57 mg / 500 mg product is similar to Endo's approved 7.5 mg oxycodone / 500 mg acetaminophen in that both products contain 6.72 mg oxycodone base.

The adult dosing of the proposed drugs is shown in Attachment 3. Dosing should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids. Oxycodone hydrochloride, oxycodone terephthalate, and acetaminophen tablets are given orally. The usual adult dosage is one tablet every six hours as needed for pain.

The total daily dose of acetaminophen should not exceed 4 grams. The maximum daily dose of oxycodone hydrochloride / oxycodone terephthalate / acetaminophen 9.25 mg / 0.85 mg / 650 mg is six tablets. The maximum daily dose of oxycodone hydrochloride / oxycodone terephthalate / acetaminophen 7.0 mg / 0.57 mg / 500 mg is eight tablets. A side by side comparison of the dosing for the reference and proposed products is enclosed as Attachment 4.

Approval of the proposed products in this suitability petition will create the possibility for the availability of oxycodone split salts with acetaminophen at the 2.25 mg oxycodone hydrochloride, 0.19 mg oxycodone terephthalate, and 325 mg acetaminophen; 4.5 mg oxycodone hydrochloride, 0.38 oxycodone terephthalate, and 325 acetaminophen; 7.0 mg oxycodone hydrochloride, 0.57 mg oxycodone terephthalate, and 500 mg acetaminophen; and 9.25 mg oxycodone hydrochloride, 0.85 mg oxycodone terephthalate, and 650 mg acetaminophen levels, thus giving physicians greater prescribing flexibility.

C. Environmental Impact

As provided in 21 C.F.R. § 25.31, neither an environmental assessment nor an environmental impact statement is required.

D. Economic Impact

As provided in 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to us which are unfavorable to the petition.

Sincerely,

KING & SPALDING
1730 Pennsylvania Avenue, NW
Washington, DC 20006
202/737-0500

By: 
Jess H. Stribling
Ellen Armentrout

Attachments

Table

Approved Products	Products for Which Suitability Petitions Have Been Approved	Proposed Products
4.5 mg oxycodone hydrochloride 0.38 mg oxycodone terephthalate 325 mg aspirin	4.5 mg oxycodone hydrochloride 0.38 mg oxycodone terephthalate 325 mg acetaminophen	9.25 mg oxycodone hydrochloride 0.85 mg oxycodone terephthalate 650 mg acetaminophen
2.25 mg oxycodone hydrochloride 0.19 mg oxycodone terephthalate 325 mg aspirin	2.25 mg oxycodone hydrochloride 0.19 mg oxycodone terephthalate 325 mg acetaminophen	7.0 mg oxycodone hydrochloride 0.57 mg oxycodone terephthalate 500 mg acetaminophen
10.0 mg oxycodone hydrochloride 650 mg acetaminophen	[redacted]	
7.5 mg oxycodone hydrochloride 500 mg acetaminophen	[redacted]	

DEPARTMENT OF HEALTH & HUMAN SERVICES

ANDA 40-341

RECEIVED

JUL 26 1999

REGULATORY AFFAIRS DEPT.
ENDO PHARMACEUTICALS INC.

Food and Drug Administration
Rockville MD 20857

JUL 26 1999

Endo pharmaceuticals, Inc.
Attention: Carol Patterson
500 Endo Blvd.
Garden City, NY 11530

Dear Madam:

This is in reference to your abbreviated new drug application dated November 9, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone and Acetaminophen Tablets USP, 7.5 mg/500 mg, respectively, and Oxycodone and Acetaminophen Tablets USP, 10 mg/650 mg, respectively.

Reference is also made to your amendments dated June 16, July I, and July 20, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling, Accordingly, the application is approved, The drug products, Oxycodone and Acetaminophen Tablets USP, 7.5 mg/500 mg and Oxycodone and Acetaminophen Tablets USP, 10 mg/650 mg, can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain Changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns, Please submit all proposed materials in draft or mock-up form, not final print.

submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Pramotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn

Douglas L. Sporn
Director
Office of Generic Prugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 16

King and Spalding
Attention: Jess Stribling
1730 Pennsylvania Avenue, N.W.
Washington, D.C. 20006-4706

Docket No. 98P-1291/CP1

Dear Mr. Stribling:

This is in response to your petition filed on December 21, 1998, and your amendments dated January 22, 1999, January 25, 1999 and July 27, 1999, requesting permission to file an Abbreviated New Drug Application (ANDA) for the following drug products: Oxycodone Hydrochloride/Oxycodone Terephthalate/Acetaminophen Tablets, 4.5 mg/0.38 mg/325mg and Oxycodone Hydrochloride/Oxycodone Terephthalate/Acetaminophen Tablets, 2.25 mg/0. 19 mg/325 mg. The listed drug products to which you refer in your petition are Percodan® (Oxycodone Hydrochloride/Oxycodone Terephthalate/Aspirin) Tablets, 4.5mg/0.38mg/325 mg, and Percodan ® Demi (Oxycodone Hydrochloride/Oxycodone Terephthalate/Acetaminophen) Tablets, 2.25 mg/0.19mg/325 mg manufactured by Endo Pharmaceuticals.

We have reviewed your petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act) and have determined that it is approved. This letter represents the Agency's determination that an ANDA may be submitted for the above-referenced drug products.

Your request involves a change in one active ingredient for another active ingredient of the same pharmacologic class in a fixed combination listed drug product [i.e., substituting an equipotent dose of acetaminophen (APAP) for aspirin (ASA) in the listed drug products]. The change you request is the type of change that is authorized under the Act.

Under Section 505@(2)(C)(i) of the Act, the Agency must approve a petition seeking a change in one active ingredient for another active ingredient of the same pharmacologic class in a fixed combination listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing active ingredient (See 21 C.F.R. §314.93(c)(1)).

According to the Tentative Final Monograph (TFM) for OTC Internal Analgesic, Antipyretic, and Antirheumatic Products published November 16, 1988 in the Federal Register (53 FR 46204) the Agency believes at this time that it is reasonable for APAP and ASA to have the same dosage and frequency of administration because, based upon the data submitted to the Panel, the safe and effective dosage ranges for APAP and ASA are the same-325 mg to 650 mg every 4 hours, not to exceed 4 g in 24 hours (TFM, 53 FR at 46235). Accordingly, the Agency finds that the change in active ingredient for the specific proposed drug products does not pose

questions of safety or effectiveness.

In addition, this petition was evaluated with respect to the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule, published in the Federal Register (Pediatric Rule)(63 FR 66632). The agency has determined that your proposed change in active ingredient is subject to the Pediatric Rule and has concluded that investigations are not necessary to demonstrate the safety and effectiveness of your proposed products in the pediatric population, because the products do not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and are not likely to be used in a substantial number of pediatric patients.

The Agency concludes, therefore, that investigations are not necessary in this instance. The pediatric study requirement is waived at this time but may be reevaluated if new information is available at the time you file your application. In addition, if shown to meet bioavailability requirements, the proposed drug products can be expected to have the same therapeutic effect as the listed reference drug products.

The approval of this petition to allow an ANDA to be submitted for the above-referenced drug products does not mean that the Agency has determined that an ANDA will be approved for the drug products. The determination of whether an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the Agency.

To permit review of your ANDA submission, you must submit all information required under Sections 505(j)(2)(A) and (B) of the Act. To be approved, the drug products will, among other things, be required to meet current bioavailability requirements under Section 505(j)(2)(A)(iv) of the Act. We suggest that you contact the Director, Division of Bioequivalence, at (301) 827-5847 to determine the specific requirements for these drug products. During the review of your application, the Agency may require the submission of additional information.

The listed drug products to which you refer in your ANDA must be the drug products upon which you based this petition. In addition, you should refer in your ANDA to the appropriate petition docket number cited above, and include a copy of this letter in the ANDA submission.

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, Room 1061, Mail Stop HFA-305, 5630 Fishers Lane, Rockville, MD 20852.

Sincerely yours,

Douglas L. Spom
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

OXYCODONE AND ACETAMINOPHEN TABLETS, USP
*7.0 mg/0.57 mg and 500 mg
**9.25 mg/0.85 mg and 650 mg

CII

R_X only

DESCRIPTION

Oxycodone and Acetaminophen Tablets contains:

Oxycodone Hydrochloride	7.0 mg*
Oxycodone Terephthalate	0.57 mg*
Acetaminophen, USP	500 mg
Oxycodone Hydrochloride	9.25 mg**
Oxycodone Terephthalate	0.85 mg**
Acetaminophen, USP	650 mg

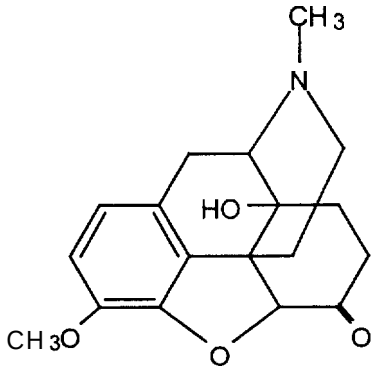
* 7.0 mg oxycodone HCl is equivalent to 6.27 mg of oxycodone.
0.57 mg oxycodone terephthalate is equivalent to 0.45 mg of oxycodone.

** 9.25 mg oxycodone HCl is equivalent to 8.29 mg of oxycodone.
0.85 mg oxycodone terephthalate is equivalent to 0.67 mg of oxycodone.

Oxycodone and Acetaminophen Tablets also contain: microcrystalline cellulose and starch.

Acetaminophen occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.

The oxycodone component is 14-hydroxydihydrocodeinone, a white, odorless, crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic opioid analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in Oxycodone and Acetaminophen Tablets are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

INDICATIONS AND USAGE

Oxycodone and Acetaminophen Tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

Oxycodone and Acetaminophen Tablets should not be administered to patients who are hypersensitive to oxycodone or acetaminophen.

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of Oxycodone and Acetaminophen Tablets, and this product should be prescribed and administered with the same degree of caution appropriate to the use of other oral opioid-containing medications. Like other opioid-containing medications, Oxycodone and Acetaminophen Tablets are subject to the Federal Controlled Substances Act (Schedule II).

PRECAUTIONS

General

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal *Conditions:* The administration of Oxycodone and Acetaminophen Tablets or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients: Oxycodone and Acetaminophen Tablets should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Oxycodone and Acetaminophen Tablets should be cautioned accordingly.

Drug Interactions

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Oxycodone and Acetaminophen Tablets may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with opioids may produce paralytic ileus.

Usage in Pregnancy

Pregnancy Category C: Animal reproductive studies have not been conducted with Oxycodone and Acetaminophen Tablets. It is also not known whether Oxycodone and Acetaminophen Tablets can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Oxycodone and Acetaminophen Tablets should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Use of opioids during pregnancy may produce physical dependence in the neonate.

Labor and Delivery: As with all opioids, administration of Oxycodone and Acetaminophen Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn and the mother, especially if higher doses are used.

Nursing Mothers

It is not known whether Oxycodone and Acetaminophen Tablets are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Oxycodone and Acetaminophen Tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus. At higher doses, oxycodone has most of the disadvantages of morphine including respiratory depression.

DRUGABUSEANDDEPENDENCE

Oxycodone and Acetaminophen Tablets are a Schedule II controlled substance.

Oxycodone can produce drug dependence and has the potential for being abused (See WARNINGS).

OVERDOSAGE

Acetaminophen

Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patient's estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural, or functional hepatic abnormalities.

Oxycodone

Signs and Symptoms: Serious overdosage with oxycodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids, including oxycodone. Therefore, an appropriate dose of naloxone hydrochloride (usual initial adult dose 0.4 mg to 2 mg) should be administered preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation (see package insert). Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids. Oxycodone and Acetaminophen Tablets, USP are given orally. The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams (maximal daily dose of Oxycodone HCl/Oxycodone Terephthalate/Acetaminophen 7.0 mg/0.57 mg/500 mg is 8 tablets and the maximal daily dose of Oxycodone HCl/Oxycodone Terephthalate/Acetaminophen 9.25 mg/0.85 mg/650 mg is 6 tablets).

HOW SUPPLIED

DEA Order Form Required.

November, 1999

~~ENDO LABORATORIES~~

~~PERCODAN®~~

~~(oxycodone and aspirin tablets, USP)~~

~~CII~~

OXYCODONE AND ACETAMINOPHEN TABLETS, USP
*7.0 mg/0.57 mg and 500 mg
**9.25 mg/0.85 mg and 650 mg

CII

R_x only

DESCRIPTION

~~Each tablet of PERCODAN contains:~~
~~Oxycodone hydrochloride 4.50 mg*~~
~~WARNING: May be habit forming~~
~~Oxycodone terephthalate 0.38 mg**~~
~~WARNING: May be habit forming~~
~~Aspirin, USP 325~~Oxycodone and Acetaminophen Tablets contains:

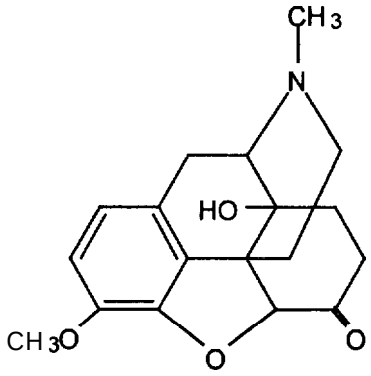
Oxycodone Hydrochloride	**7.0** mg*
Oxycodone Terephthalate	**0.57** mg*
Acetaminophen, USP	**500** mg
Oxycodone Hydrochloride	9.25 mg**
Oxycodone Terephthalate	**0.85** mg**
Acetaminophen, USP	**650** mg

~~*4.50*~~ 7.0 mg oxycodone HCl is equivalent to ~~4.0338~~6.27 mg of oxycodone.
~~**0.38~~ 0.57 mg oxycodone terephthalate is equivalent to 0.45 mg of oxycodone.
** 9.25 mg oxycodone HCl is equivalent to 8.29 mg of oxycodone.
~~0.3008~~ 0.85 mg oxycodone terephthalate is equivalent to 0.67 mg of oxycodone.

~~PERCODAN~~Oxycodone and Acetaminophen Tablets also contain: ~~D&C Yellow 10, FD&C Yellow 6,~~ microcrystalline cellulose and starch.

Acetaminophen occurs as a white, odorless, crystalline powder, possessing a **slightly** bitter taste.

The oxycodone component is 14-hydroxydihydrocodeinone, a ~~white odorless~~white, odorless, crystalline powder ~~which~~having a saline, bitter taste. It is derived from the opium alkaloid, thebaine, and may be represented by the following structural formula:



~~**ACTIONS**~~

CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic ~~narcotic~~opioid analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in ~~PERCODAN~~Oxycodone and Acetaminophen Tablets are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

~~PERCODAN also contains the non-narcotic antipyretic analgesic, aspirin.~~

~~**INDICATIONS**~~

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

INDICATIONS AND USAGE

~~For~~Oxycodone and Acetaminophen Tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

~~Hypersensitivity~~Oxycodone and Acetaminophen Tablets should not be administered to patients who are hypersensitive to oxycodone or ~~aspirin.~~acetaminophen.

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of ~~PERCODAN, and it~~Oxycodone and Acetaminophen Tablets, and this product should be prescribed and administered with the same degree of caution appropriate to the use of other oral

~~narcotic-containing~~opioid-containing medications. Like other ~~narcotic-containing~~opioid-containing medications, ~~PERCODAN is~~Oxycodone and Acetaminophen Tablets are subject to the Federal Controlled Substances Act (Schedule II).

~~**Usage in ambulatory patients:** Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN should be cautioned accordingly.~~

~~**Interaction with other central nervous system depressants:** Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.~~

~~**Usage in pregnancy:** Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.~~

~~**Pediatric Use:** PERCODAN should not be administered to pediatric patients. PERCODAN®-Demi, containing half the amount of oxycodone, can be considered. (See product prescribing information for PERCODAN-Demi.)~~

~~**Reye Syndrome** is a rare but serious disease which can follow flu or chicken pox in children and teenagers. While the cause of Reye Syndrome is unknown, some reports claim aspirin (or salicylates) may increase the risk of developing this disease.~~

~~Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.~~

PRECAUTIONS

General

Head ~~**injury and increased intracranial pressure:**~~*Injury and Increased Intracranial Pressure:* The respiratory depressant effects of ~~narcotics~~opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, ~~narcotics~~opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute ~~**abdominal conditions:**~~*Abdominal Conditions:* The administration of ~~(oxycodone and aspirin) or other narcotics~~Oxycodone and Acetaminophen Tablets or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special ~~**risk patients: PERCODAN**~~*Risk Patients:* Oxycodone and Acetaminophen Tablets should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Oxycodone and Acetaminophen Tablets should be cautioned accordingly.

Drug Interactions
Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Oxycodone and Acetaminophen Tablets may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with opioids may produce paralytic ileus.

Usage in Pregnancy
Pregnancy Category C: Animal reproductive studies have not been conducted with Oxycodone and Acetaminophen Tablets. It is also not known whether Oxycodone and Acetaminophen Tablets can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Oxycodone and Acetaminophen Tablets should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Use of opioids during pregnancy may produce physical dependence in the neonate.

Labor and Delivery: As with all opioids, administration of Oxycodone and Acetaminophen Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn and the mother, especially if higher doses are used.

Nursing Mothers
It is not known whether Oxycodone and Acetaminophen Tablets are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Oxycodone and Acetaminophen Tablets are administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus. At higher doses, oxycodone has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

~~PERCODAN tablets~~Oxycodone and Acetaminophen Tablets are a Schedule II controlled substance.
~~substance.~~
Oxycodone can produce drug dependence and has the potential for being abused (See WARNINGS).

OVERDOSAGE

Acetaminophen

Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patient's estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural, or functional hepatic abnormalities.

Oxycodone

Signs and Symptoms: Serious overdosage with oxycodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific

antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids, including oxycodone. Therefore, an appropriate dose of naloxone hydrochloride (usual initial adult dose 0.4 mg to 2 mg) should be administered preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation (see package insert). Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of ~~narcotics.~~opioids. ~~PERCODAN is~~Oxycodone and Acetaminophen Tablets, USP are given orally. The usual adult dosage is one tablet every 6 hours as needed for ~~pain.~~
pain. The total daily dose of acetaminophen should not exceed 4 grams (maximal daily dose of Oxycodone HCl/Oxycodone Terephthalate/Acetaminophen 7.0 mg/0.57

~~**DRUG INTERACTIONS**~~

~~The CNS depressant effects of PERCODAN may be additive with that of other CNS depressants (See WARNINGS).~~

~~Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effects of uricosuric agents.~~

~~**MANAGEMENT OF OVERDOSAGE**~~

~~**Signs and Symptoms:** Serious overdose with PERCODAN is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of PERCODAN may, in addition, result in acute salicylate intoxication.~~

~~**Treatment:** Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride (NARCAN®) is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics including oxycodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered (usual initial adult dose 0.4 mg-2 mg) preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.~~

~~Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.~~

~~Gastric emptying may be useful in removing unabsorbed drug.~~

mg/500 mg is 8 tablets and the maximal daily dose of Oxycodone HCl/Oxycodone Terephthalate/Acetaminophen 9.25 mg/0.85 mg/650 mg is 6 tablets).

HOW SUPPLIED

~~PERCODAN (4.50 mg oxycodone hydrochloride, 0.38 mg oxycodone terephthalate, 325 mg Aspirin, USP), supplied as a yellow tablet, with one face scored and inscribed "PERCODAN" and plain on the other side is available in:~~

~~Bottles of 100 NDC 63481-135-70~~
~~Bottles of 500 NDC 63481-135-85~~
~~Hospital blister pack of 25 NDC 63481-135-75~~
~~(in units of 100 tablets)~~

~~Store at controlled room temperature 15°-30°C (59°-86°F).~~

DEA Order Form Required.

~~**CAUTION:** Federal (USA) law prohibits dispensing without prescription.~~

~~Manufactured for:~~
~~**Endo Pharmaceuticals Inc.**~~
~~Chadds Ford, Pennsylvania 19317~~

~~Manufactured by:~~
~~DuPont Pharma~~
~~Wilmington, Delaware 19880~~

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